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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/051,497	01/18/2002	Rong-Hwa Lin	13062-003001	1774

26161 7590 10/27/2004

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EXAMINER	
GAMBEL, PHILLIP	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 10/27/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/051,497	LIN ET AL.	
	Examiner	Art Unit	
	Phillip Gambel	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *3/10/04; 7/22/04*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) *7-9 and 27-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 10-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election of species (B), drawn to methods using an anti-PSGL-1 antibody and an agent that binds to the antibody and induces the cross-linking of a plurality of PSGL-1 antigens on the cell surface without traverse in the Reply, filed 7/22/04.

Previously, applicant elected the species autoimmune disease and type I diabetes in the Reply, filed 3/10/04.

Claims 1-6 and 10-26 are under consideration in the instant application.

Claims 7-9 and 27-37 have been withdrawn from consideration by the examiner 37 CFR 1.142(b), as being drawn to a nonelected invention or species.

2. The filing date of the instant claims as they read on "methods of preventing or reducing a T cell-mediated immune responses in an individual, including the "selecting an individual diagnosed", "administering a compound ... induces a signal transduction pathway that results in the death of the T cell" (e.g. claim 1), "an agent that binds to the monoclonal antibody and induces the cross-linking of a plurality of PSGL-1 antigens on the surface of the T cell" (e.g. claim 4), detecting the number of T cells in a first biological sample (e.g. claims 13-14), "20% of peripheral blood $CD3^+$ cells (e.g. claims 15-16) and "diabetes" (e.g. elected autoimmune disease) is deemed to be the filing date of the instant application USSN 10/051,497, filed 8/3/01, as the previous provisional priority application does not appear to provide sufficient written description for the claimed "limitations" indicated herein.

If applicants disagree, applicants should present a detailed analysis as to why the claimed subject matter has clear support in the parent application. Applicant is invited to verify the priority date of the instant claims, including written support and enablement under 35 USC 112, first paragraph.

3. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Applicant should restrict the title to the claimed invention.

4. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected.

"BALB/c" is the proper designation of this mouse species (e.g. see page 24, line 8 of the specification).

Trademarks should be capitalized or accompanied by the ™ or ® symbol wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Appropriate corrections are required

5. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6 This is a rejection under 35 USC § 112, first paragraph, "written description" (and not new matter).

Claims 1, 4—6, 10-15, 17 and 20-26 are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed.

There is insufficient written description encompassing "a compound that binds to PSGL-1" and an agent that binds to the monoclonal antibody and induces the cross-linking of a plurality of PSGL-1 antigens on the surface of T cell" because the relevant identifying characteristics such as structure of other physical and/or chemical characteristics of both the "compound that binds to PSGL-1" and the "agent that binds to the monoclonal antibody", are not set forth in the specification as filed, commensurate in scope with the claimed invention.

It is noted that the specification as filed provides for anti-PSGL-1 antibodies as compounds that bind to PSGL-1 (e.g. see pages 9-12 of the instant specification) and provides for screening assays for compounds that modulate PSGL-1 function (e.g., see pages 12-15 of the specification).

Applicant is relying upon certain biological activities and the disclosure of a limited representative number of species of "compounds which bind PSGL-1", namely anti-PSGL-1 antibodies and screening assays, computer modeling and searching technologies to support an entire genus of diverse and unrelated molecules and physiological / immunological pathways. The instant invention encompasses any "compound" that binds PSGL-1, yet the instant specification does not provide sufficient written description as to the structural features of said "compounds" and the correlation between the chemical structure and the desired binding and immunological function.

Applicant is relying upon the disclosure of the anti-hamster Ig as a cross-linker antibody (e.g. see Example 3 on pages 19-20) to support an entire genus of "agents that bind to an anti-PSGL-1 antibody". This invention encompasses any "agent that binds to the monoclonal antibody and induces the cross-linking of a plurality of PSGL-1 antigens on the surface of cell" (e.g. see Summary of the Invention, particularly page 5, paragraph 3 of the instant specification), yet the instant specification does not provide sufficient written description as to the structural features of said "agents" and the correlation between the chemical structure and the desired binding and immunological function.

It appears that the claims encompass both "compounds" and "agents" which rely upon a myriad of distinct and diverse structures and do not encompass common structural elements essential to the

common utility of "a compound that binds to PSGL-1" and an agent that binds to the monoclonal antibody and induces the cross-linking of a plurality of PSGL-1 antigens on the surface of T cell".

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Thus, the specification fails to describe these DNA sequences. The Court further elaborated that generic statements are not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. Finally, the Court indicated that while applicants are not required to disclose every species encompassed within a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, defined by nucleotide sequence, falling within the scope of the genus, See The Regents of the University of California v. Eli Lilly and Company, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Mere idea or function is insufficient for written description; isolation and characterization at a minimum are required.

"Adequate written description requires a precise definition, such as by structure, formula, chemical name or physical properties, not a mere wish or plan for obtaining the claimed chemical invention." Id. at 1566, 43 USPQ2d at 1404 (quoting Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606). Also see Enzo-Biochem v. Gen-Probe 01-1230 (CAFC 2002).

The disclosure must describe the invention with particularity and convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. Knowing the starting point is not enough, that is little more than a research plan.

The instant claims do not provide sufficient structural and functional characteristics coupled with a known or disclosed correlation between function and structure. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus of "a compound that binds to PSGL-1" and "an agent that binds to the monoclonal antibody and induces the cross-linking of a plurality of PSGL-1 antigens on the surface of T cell".

The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species; then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 column 3).

In the absence of structural characteristics that are shared by members of the genus of "a compound that binds to PSGL-1" and an agent that binds to the monoclonal antibody and induces the cross-linking of a plurality of PSGL-1 antigens on the surface of T cell"; one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. See University of California v. Eli Lilly and Co. 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997).

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

7. Claims 1, 4—6, 10-15, 17 and 20-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for "anti-PSGL-1 antibodies" and anti-hamster Ig", does not reasonably provide enablement for any "compound that binds to PSGL-1" and any "agent that binds to the monoclonal antibody and induces the cross-linking of a plurality of PSGL-1 antigens on the surface of T cell"

The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and use the invention commensurate in scope with these claims. molecule

A) "compound that binds to PSGL-1":

It is noted that the specification as filed provides for anti-PSGL-1 antibodies as compounds that bind to PSGL-1 (e.g. see pages 9-12 of the instant specification) and provides for screening assays for compounds that modulate PSGL-1 function (e.g., see pages 12-15 of the specification).

Applicant is relying upon certain biological activities and the disclosure of a limited representative number of species of "compounds which bind PSGL-1", namely anti-PSGL-1 antibodies and screening assays, computer modeling and searching technologies to support an entire genus of diverse and unrelated molecules and physiological / immunological pathways. The instant invention encompasses any "compound" that binds PSGL-1, yet the instant specification does not provide sufficient guidance and direction on as to the structural features of said "compounds" and the correlation between the chemical structure and the desired binding and immunological function.

Applicant has not provided sufficient biochemical information (e.g. molecular weight, amino acid composition, N-terminal sequence, etc.) that distinctly identifies the "compounds which bind PSGL-1" other than "anti-PSGL-1 antibodies". "A compound which binds PSGL-1" may have some notion of the desired function and target specificity of the claimed "compound". However, the recitation and disclosure of "compound that binds PSGL-1" fails to provide sufficient direction and guidance as to the key or critical structural attributes and characteristics of the claimed "compounds". It appears that the claims encompass "compounds" which rely upon a myriad of distinct and diverse structures and do not encompass common structural elements essential to the common utility of "a compound that binds to PSGL-1".

The instant disclosure does not provide for sufficient guidance and direction towards the relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus of "compounds that bind PSGL-1".

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. The specification does not describe nor enable any "compound that binds PSGL-1".

While applicant relies upon the disclosure of "anti-PSGL-1 antibodies" and "screening assays, computer modeling and searching technologies", this description without more precise guidelines amount to little more that a starting point, a direction for further research. The specification provides for a plan or an invitation for those of skill in the art to experiment practicing the claimed invention but does not provide sufficient guidance or specificity as to how to execute that plan. It provides a starting point from which one of skill in the art can perform further research in order to practice the claimed invention, but this is not adequate to constitute enablement in that will enable any person skilled in the art to make and use the invention

"It is not sufficient to define the recombinant molecule by its principal biological activity, e.g. having protein A activity, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property." Colbert v. Lofdahl, 21 USPQ2d, 1068, 1071 (BPAI 1992).

Without sufficient guidance, making and using an "compound that binds PSGL-1"other than the "anti-PSGL-1 antibody" disclosed in the specification as filed as the "compound" employed in the claimed methods would have been unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

B) "agent that binds to the monoclonal antibody and induces the cross-linking of a plurality of PSGL-1 antigens on the surface of T cell":

Applicant is relying upon the disclosure of the anti-hamster Ig as a cross-linker antibody (e.g. see Example 3 on pages 19-20) to support an entire genus of "agents that bind to an anti-PSGL-1 antibody". This invention encompasses any "agent that binds to the monoclonal antibody and induces the cross-linking of a plurality of PSGL-1 antigens on the surface of cell" (e.g. see Summary of the Invention, particularly page 5, paragraph 3 of the instant specification), yet the instant specification does not provide sufficient written description as to the structural features of said "agents" and the correlation between the chemical structure and the desired binding and immunological function.

Applicant has not provided sufficient biochemical information (e.g. molecular weight, amino acid composition, N-terminal sequence, etc.) that distinctly identifies the "agent that binds to the monoclonal antibody and induces the cross-linking of a plurality of PSGL-1 antigens on the surface of T cell" other than the disclosure of the anti-hamster Ig as a cross-linker antibody (e.g. see Example 3 on pages 19-20 of the instant specification). An "agent that binds to the monoclonal antibody and induces the cross-linking of plurality of PSGL-1 antigens on the surface of T cell" may have some notion of the desired function and target specificity of the claimed "agent".

However, the recitation and disclosure of "agent" fails to provide sufficient direction and guidance as to the key or critical structural attributes and characteristics of the claimed "agents". The instant disclosure provides for insufficient guidance and direction towards the relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus of "agent that binds to the monoclonal antibody and induces the cross-linking of plurality of PSGL-1 antigens on the surface of T cell".

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. The specification does not describe nor enable any "agent that binds to the monoclonal antibody and induces the cross-linking of a plurality of PSGL-1 antigens on the surface of T cell"

While applicant relies upon the disclosure of the anti-hamster Ig as a cross-linker antibody (e.g. see Example 3 on pages 19-20) and the apparent limited disclosure of any "agent that binds to the monoclonal antibody and induces the cross-linking of a plurality of PSGL-1 antigens on the surface of T cell" (e.g. see Summary of the Invention), this description without more precise guidelines amount to little more that a starting point, a direction for further research. With respect to "agents", the specification does not appear to even provide for a plan or an invitation for those of skill in the art to experiment practicing the claimed invention and does not provide sufficient guidance or specificity as to the nature of "agents" other than the exemplified "anti-hamster Ig". This is not adequate to constitute enablement in that will enable any person skilled in the art to make and use the invention

"It is not sufficient to define the recombinant molecule by its principal biological activity, e.g. having protein A activity, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property." Colbert v. Lofdahl, 21 USPQ2d, 1068, 1071 (BPAI 1992).

Without sufficient guidance, making and using an "agent that binds to the monoclonal antibody and induces the cross-linking of plurality of PSGL-1 antigens on the surface of T cell" other than the "anti-hamster Ig" disclosed in the specification as filed as the "agent" in the claimed methods would have been unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

Without sufficient guidance, making and using an "agent that binds to the monoclonal antibody and induces the cross-linking of plurality of PSGL-1 antigens on the surface of T cell" other than the "anti-hamster Ig" disclosed in the specification as filed as the "agent" in the claimed methods would have been unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

8. Claims 1-6 and 10-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of reducing T cell mediated immune responses in an individual (including method of treating diabetes as the elected invention) and methods of inducing death of a T cell or a NK cell with anti-PSGL-1 antibodies in vivo (the elected invention), does not reasonably provide enablement for methods of "preventing diabetes" nor "methods of preventing or reducing T cell mediated immune responses in an individual (i.e. in vivo, clinically) with "agent that binds to the monoclonal antibody and induces the cross-linking of plurality of PSGL-1 antigens on the surface of T cell", including the use of the exemplified "anti-hamster Ig".

The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and use the invention commensurate in scope with these claims.

In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Since the therapeutic indices of immunosuppressive drugs or biopharmaceutical drugs can be species- and model-dependent, it is not clear that reliance on the in vitro experimental accurately reflects the relative efficacy of the claimed therapeutic strategies which relies upon an "agent that binds to the monoclonal antibody and induces the cross-linking of plurality of PSGL-1 antigens on the surface of T cell" , which encompass preventing T cell mediated immune response as it reads on preventing an autoimmune disease such as diabetes as well as cross-linking anti-PSGL-1 in vivo.

Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

The specification does not adequately teach how to effectively treat any T cell mediated immune response in an individual, including the elected autoimmune diseases and diabetes or reach any therapeutic endpoint in humans by administering "anti-PSGL-1 antibody" and an "agent that binds to the monoclonal antibody and induces the cross-linking of plurality of PSGL-1 antigens on the surface of T cell", including the use of the exemplified "anti-hamster Ig" that results in a signal transduction pathway that results in the death of a T cell.

The specification does not teach how to extrapolate data obtained from in vitro binding inhibition assays to the development of effective in vivo human therapeutic methods, commensurate in scope with the claimed invention. Experimental protocols usually are conducted under defined conditions wherein the antagonist and the stimulus/insult occur at the same or nearly the same time. Immunosuppression is much easier to achieve under such controlled conditions that experienced in the human immunoregulatory diseases such as autoimmunity targeted by the claimed invention. With respect to in vivo studies, animal models validate concepts based on studies of human disease, such studies are limited to the "acute" as opposed to "chronic" nature of the disease. In animal models, the onset of inflammation is rapid with an aggressive destructive process, whereas in humans the disease progresses more slowly, often with natural periods of disease exacerbation and remission.

As indicated above in Section 7, applicant relies upon the disclosure of the anti-hamster Ig as a cross-linker antibody (e.g. see Example 3 on pages 19-20) and the apparent mere disclosure of any "agent that binds to the monoclonal antibody and induces the cross-linking of a plurality of PSGL-1 antigens on the surface of T cell" (e.g. see Summary of the Invention). This description without more precise guidelines amount to little more that a starting point, a direction for further research. With respect to "agents", the specification does not appear to even provide for a plan or an invitation for those of skill in the art to experiment practicing the claimed invention and does not provide sufficient guidance or specificity as to the nature of "agents" other than the exemplified "anti-hamster Ig". This is not adequate to constitute enablement in that will enable any person skilled in the art to make and use the invention

Further, it is noted that Examples 6-8 on pages 22-25 of the instant specification which rely upon the administration of anti-PSGL-1 antibodies do not rely upon the administration of an "agent that binds to the monoclonal antibody and induces the cross-linking of plurality of PSGL-1 antigens on the surface of T cell".

The instant specification does not appear to provide sufficient guidance as to how to make and use such "agents" to achieve the prevention or reduction of T cell-mediated immune response in an individual. For example, PSGL-1 is expressed on a number of cell types, including essentially all blood leukocytes, including neutrophils, monocytes and lymphocytes. Also, the ability of PSGL-1 to mediate interactions between P-selectin and other cells have yielded variable and conflicting results. As indicated above in Sections 6-7, there is a lack of sufficient guidance and direction as to the nature of "agent" indicated in the instant application under the 35 USC 112, first paragraph, written description and enablement.

For example, the anti-hamster Ig cross-linking agent exemplified in the specification as filed was only employed under defined in vitro conditions and not under in vivo conditions. A sufficient amount of anti-hamster Ig would not have been expected to reach and cross-link anti-PSGL-1 antibody resulting in the death of T cells and NK cells encompassed by the claims and intended by the specification.

For example, anti-PSGL-1 antibodies would have been expected to bind a number of cells types and not just anti-PSGL-1 antibodies that bind PSGL-1 expressed on T cells. The administration of "anti-hamster Ig" would likely have resulted in eliciting neutralizing antibodies in the individual under treatment. It would have been unpredictable at the time the invention was made that an "agent, including as anti-hamster Ig", would have reached the targeted T cell populations in sufficient quantity and quality to cross-link anti-PSGL antibodies on said T cells and, in turn, result in T cell death. Applicant has not provided sufficient working examples to support this assertion and disclosure. As indicated, the instant Examples do not rely upon the claimed methods which rely upon a secondary agent.

Further, autoimmune diseases just as diabetes are diagnosed after the patient has the condition. Applicant has not provided sufficient direction and guidance as how to "prevent" an autoimmune condition, including diabetes by the claimed methods.

Given the relative incomplete understanding in the biotechnological field involved, and the lack of a reasonable correlation between the narrow disclosure in the specification and the broad scope of protection sought in the claims, a rejection under 35 USC 112, first paragraph for lack of enablement is appropriate

With respect to the administration of anti-PSGL-1 antibodies in the absence of a secondary cross-linking agent, it is noted that the mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. While it is acknowledged that the administration of anti-PSGL-1 antibodies can inhibit a variety of cell interactions and immune responses, it is unclear whether the administration of anti-PSGL-1 antibodies alone in the absence of cross-linking results in the death of a T cell, as currently recited in the instant claims. The Office is not equipped to conduct comparisons.

Applicant is invited to provide clarity as the mechanism of action by which the administration of anti-PSGL-1 antibodies can prevent or reduce T cell mediated immune responses, including autoimmunity such as diabetes in the absence of a secondary cross-linking agent.

Again, the in vivo Examples 6-8 disclosed in the specification as filed do not appear to provide objective evidence for the death of T cells. Rather these Examples simply measure depletion of T cells and transplant rejection and not T cell death in the context of the in vivo administration of anti-PSGL-1 antibodies, particularly the administration of anti-PSGL-1 antibodies in the absence of a cross-linking agent.

There is insufficient objective evidence that the skilled artisan would predict that administering "an agent that binds to the monoclonal antibody and induces the cross-linking of a plurality of PSGL-1 antigens on the surface of T cell" can result in the reduction or prevention of T cell-mediated immune responses in vivo or anti-PSGL-1 antibodies can prevent autoimmune diseases, including preventing diabetes, as the elected invention.

In view of the lack of predictability of the art to which the invention pertains the lack of established clinical protocols for effective cross-linking anti-PSGL-1- antibodies in vivo resulting in T cell death or preventing autoimmune diseases, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for reducing or preventing T cell mediated immune responses, including the administration of "an agent that binds to the monoclonal antibody and induces the cross-linking of a plurality of PSGL-1 antigens on the surface of T cell" or to prevent autoimmune diseases, including preventing diabetes, as the elected invention.

9. Claims 11-12, 15-16 and 23-24 are objected to because "$CD3^{+}$", "$CD4^{+}$" and "$CD8^{+}$" are the proper designations of "CD3+", "CD4+" and "CD8+"

10. Claims 13-14 and 25-26 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 13-14 and 25-26 are indefinite in that they do not set forth clearly the method steps to carry out "the claimed methods of "detecting the number of T cells in a first biological sample", "detecting a biological activity of T cells in a first biological sample" and "assessing viability". The claims are incomplete as they omit essential steps and endpoints to carry out the claimed methods of detection.

Applicant is invited to amend the claims to recite the appropriate steps to carry out the claimed methods

B) Further, claims 14 and 26 are indefinite in the recitation of "detecting a biological activity" because the nature of the biological activity is ill-defined and ambiguous.

Applicant is invited to amend the claims to recite a clear measure of the intended targeted biological activity which is supported by the written description of the specification as-filed.

C) Applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter. See MPEP 714.02 and 2163.06.

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office Action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

13. For examination purposes, it appears that claimed methods which rely upon the elected species of administering an anti-PSGL-1 antibody and an "agent that binds to the monoclonal antibody and induces the cross-linking of plurality of PSGL-1 antigens on the surface of T cell appears free of the prior art.

Accordingly, the prior art rejections has been extend to read on the species of administering anti-PSGL-1 antibodies in the absence of administering a secondary "cross-linking agent".

As indicated in the prior art rejections that follow, it does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosures of administering anti-PSGL-1 antibodies to inhibit P-selectin- / PSGL-1-mediated interactions, including immune responses such as the elected autoimmune disease diabetes. However, the prior art disclosures are silent on the claimed recitation of "inducing a signal transduction pathway that results in the death of a T cell or NK cell".

As pointed out above, the Office is not equipped to conduct comparisons. Applicant is invited to provide clarity as the mechanism of action by which the administration of anti-PSGL-1 antibodies can prevent or reduce T cell mediated immune responses, including autoimmunity such as diabetes in the absence of a secondary cross-linking agent.

14. Claims 1-3, 6, 10-12, 15-19 and 22-24 are rejected under 35 U.S.C. § 102(b) as being anticipated by Larsen et al. (U.S. Patent No. 5,840,679) (see entire document). (SEE 1449)

Larsen et al. teaches methods of treating conditions characterized by P-selectin mediated intercellular adhesion, including inflammatory conditions, autoimmune conditions such as diabetes (see columns 15-16, overlapping paragraph) with neutralizing anti-PSGL-1 antibodies, including monoclonal antibodies (e.g. see column 18, paragraphs 2-4).

Although the reference is silent about the induction of T cell or NK cell death as well as identifying the T cell as activated, $CD3^+$, $CD4^+$, or $CD8^+$ as well as the depletion of T cells, it does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001). "{i}t is a general rule that merely discovering and claiming a new benefit of an old process cannot render the process again patentable." In re Woodruff, 16 USPQ2d 1934, 1936 (Fed. Cir. 1990). The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See MPEP 2145.

Although the reference is silent about selecting an individual diagnosed as having or as being at risk of acquiring a condition characterized by an excessive or unwanted T cell-mediated immune response, such limitations are anticipated by the targeted conditions and diseases described in columns 15-16, overlapping paragraph, because the ordinary artisan would have had to diagnose a patient with such a condition or disease in order to treat said condition or disease.

Also, a species will anticipate a claim to a genus. See MPEP 2131.02.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations, including the targeted cell populations and the mechanism of action, would be inherent properties of the referenced methods to treat a number of conditions and diseases with anti-PSGL-1 antibodies, which block the P-selectin ligand adherence function, abolish or markedly reduce inflammation (e.g. see columns 18-19, overlapping paragraph). Here, too, it is noted that target cells targeted by anti-PSGL-1 antibody may eliminated by ADCC (see column 19, lines 5-13).

Also, the Courts have held that there is no requirement that those of ordinary skill in the art know of the inherent property. See MPEP 2131.01(d) and MPEP § 2112 - § 2113 for case law on inherency.

It does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001

15. Claims 1-3, 6 and 10-19, and 22-26 are rejected under 35 U.S.C. § 103(a) as being unpatentable over by Larsen et al. (U.S. Patent No. 5,840,679) in view of Trembleau et al. (J. Immunol. 163 : 2960 – 2968, 1999), Yago et al. (J. Immunol. 161 : 1140 –1145 (1998), Hirata et al. (J. Exp. Med. 192: 1669 – 1675, 2000) and Cobbold et al. (U.S. Patent No. 6,056,956).

Larsen et al. teaches methods of treating conditions characterized by P-selectin mediated intercellular adhesion, including inflammatory conditions, autoimmune conditions such as diabetes (see entire document, including columns 15-16, overlapping paragraph) with neutralizing anti-PSGL-1 antibodies, including monoclonal antibodies (e.g. see column 18, paragraphs 2-4).

Although the reference is silent about the induction of T cell or NK cell death as well as identifying the T cell as activated, $CD3^+$, $CD4^+$, or $CD8^+$ as well as the depletion of T cells per se, it does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001). "{i}t is a general rule that merely discovering and claiming a new benefit of an old process cannot render the process again patentable." In re Woodruff, 16 USPQ2d 1934, 1936 (Fed. Cir. 1990). The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See MPEP 2145.

Further, the reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. See MPEP 2144.

Also, it is not a requirement that an inventor set forth or even know how or why the invention works. Newman v. Quigg, 11 USPQ2d 1340 (Fed. Cir. 1989).

Therefore, the prior art clearly provides for the administration of anti-PSGL-1 antibody to inhibit adhesion via PSGL-1/P-selectin interactions, inflammation and autoimmunity, including diabetes (elected species). While the prior art does not explicitly teach the induction of T cell or NK cell death, the prior art clearly provides for the same or nearly the same desired endpoints by administering the same antagonists to the same patient populations encompassed by the claimed methods. Again, it does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure

Although the reference is silent about selecting an individual diagnosed as having or as being at risk of acquiring a condition characterized by an excessive or unwanted T cell-mediated immune response, such limitations are expected by the targeted conditions and diseases described in columns 15-16, overlapping paragraph of Larsen et al., because the ordinary artisan would have had to diagnose a patient with such a condition or disease in order to treat said condition or disease.
Larsen et al. differs from the claimed methods by not disclosing the art known monitoring of T cells and NK cells in therapeutic methods.

Trembleau et al. teach T cell recruitment in the pancreas favored by IL-12-deficient NOD mice, as revealed by increased P-selectin ligand expression on pancreas-infiltrating T cells and, this could, at least in part, compensate for the defective Th1 cell pool recruitable from peripheral lymphoid organs (see entire document, including the Abstract and Discussion). Also, this reference discusses the role of T cells in autoimmunity, including diabetes (see Introduction and Discussion).

Hirata et al. teach PSGL-1 mediated T helper lymphocyte migration in inflammation (see entire document, including the Abstract, Results and Discussion). The Results, including the Figures provide for monitoring the expression and function of PSGL-1-expressing T cells (see pages 1670-1674).

Yago et al. teach the role of PSGL-1/Pselectin interactions in the adhesion of NK cells, including the ability of anti-PSGL-1 antibodies to abolish such interactions (See entire document, including the Abstract and Discussion). Yago et al. teach the art known role of NK cells in various immune responses (see Introduction and Discussion).

Cobbold et al. teach monitoring T cell subsets and activities (e.g. mixed lymphocyte cultures) from individuals whom have been treated with immunosuppressive antibodies (see entire document, including columns 12-21, Tolerance and Anergy in Mice Grafted with Multiple Minor Antigen Mismatched Bone Marrow, Monitoring T cell Subsets for Depletion and Mixed Lymphocyte Cultures, The Effects of Combined Rat IgG2b Antibodies on Circulating T Cells, Tolerant Mice Can Still Respond In Vitro as well as Tables 2, 3, 4, 7 and 9).

Given the teachings of the prior art that PSGL-1 was expressed on T cells, including T cells involved in inflammation and autoimmunity such as diabetes, as taught by Trembleau et al. and Hirata et al. in conjunction with the teachings of treating inflammation with anti-PSGL-1 antibodies as taught by Larsen et al., the ordinary artisan would have been motivated to monitor the presence and function of T cells as a result of anti-PSGL-1 treatment. Hirata et al. and Cobbold et al. both teach monitoring T cell numbers and function in response to the administration of antagonistic antibodies in vivo, including the administration of anti-PSGL-1. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to detect the number, viability and biological activity of T cells prior to and after the administration of an antagonistic anti-PSGL-1 antibody in inflammatory or autoimmune conditions such as diabetes to monitor the efficacy of antibody treatment, including measuring the control values prior to treatment.

Note that Cobbold et al. teach that it may be necessary to reduce a population of T cells to less than about 70% - 10% of their normal values in order to achieve the desired immunosuppressive endpoint (see column 4, paragraph 2).

Hirata et al. teach that the administration of anti-PSGL-1 antibodies could reduce the number of T cells migrating into an inflamed skin by 66% (see page 1672, Migration of PSGL-1deficient Th1 Cells into the Inflamed Skin is Impaired).

Therefore, one of ordinary skill in the art would have had an expectation of success that the administration of antagonistic antibodies, including antibodies that bind T cells or NK cells, including anti-PSGL-1 antibodies, could reduce T cell populations by at least 20% or that anti-PSGL-1 antibody can abolish NK binding to P-selectin. Given that PSGL-1 is expressed on activated, $CD4^+$, $CD8^+$ T cells as well as NK cells targeted by anti-PSGL-1 antibody, one of ordinary skill in the art would have had sufficient motivation and expectation of success in monitoring the number, activity and viability of various targeted cells by the administration of anti-PSGL-1 antibodies in order to assess the efficacy of the treatment and the immune responses and capabilities of the patient, as indicated by Trembleau et al., Hirata et al. and Cobbold et al.. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

16. No claim allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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October 21, 2004